PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS & PATENT INTERFERENCES

Applicants:	R.K. Bakshi, et al.
Serial No.:	09/990,499 (Case No. 20385YDA)
Filed:	November 21, 2001
For:	SUBSTITUTED PIPERIDINES AS MELANOCORTIN-4 RECEPTOR AGONISTS

Art Unit: 1625

Examiner: D. M. Seaman

Assistant Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

The present Brief is submitted in triplicate under the provisions of 37 C.F.R. 1.192 in support of an appeal from the final rejection of the above-cited application dated August 9, 2002. The Notice of Appeal was timely filed on November 8, 2002. Accompanying the Brief on Appeal is a petition for extension of time, the period for submission of the Brief on Appeal having been extended one month from January 8, 2003 to February 8, 2003. Appellants hereby respectfully seek to have the rejections of pending Claims 39-75 overturned.

REAL PARTY IN INTEREST

The present application has been assigned to Merck & Co., Inc. of Rahway, New Jersey, by assignment recorded at the U.S. Patent and Trademark Office on January 8, 2002 (Reel 012461/Frame 0891). The inventors on the application assigned their interests to Merck & Co., Inc., in an assignment executed May 23, 2000; May 24, 2000; May 25, 2000; and June 9, 2000.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the Appellants, or known to Appellants' legal representative, that will directly affect the Board's decision in the pending appeal.

STATUS OF CLAIMS

The Claims pending as of the time of the Final Rejection are Claims 39-75, which constitute the Claims being appealed. A complete set of the Claims under appeal is provided in the accompanying Appendix.

STATUS OF AMENDMENTS

No amendment was filed in response to the Final Rejection dated August 9, 2002, of the Claims as amended under 37 C.F.R. 1.111 on June 4, 2002, in response to the Office Action dated March 11, 2002.

SUMMARY OF THE INVENTION

The present invention defined in Claims 39-73 under appeal relates to novel methods of treating male erectile dysfunction (MED) with selective agonists of the human melanocortin-4 receptor (MC-4R). Claims 74-75 are directed to methods for the oral treatment of MED with selective agonists of the human MC-4R.

ISSUES

The issue presented for review by the Board of Appeals is the rejection under 35 U.S.C. § 112, first paragraph, of Claims 39-75 as being unpatentable for lack of enablement as to how to make and/or use the claimed invention.

GROUPING OF CLAIMS

For the purpose of this Appeal, the Claims shall be grouped as follows:

Group I: Claims 39-73
Group II: Claims 74-75

The Claims of Groups I and II are considered to be separately patentable and do not stand or fall together. The Claims of Group I are directed to methods of treating male erectile dysfunction with selective human MC-4R agonists. The Claims of Group II are limited to methods for the oral treatment of male erectile dysfunction comprising the oral administration of a selective human MC-4R agonist.

ARGUMENT

The Claims of Group I are directed to methods of treating male erectile dysfunction by administering a therapeutically effective amount of a selective human MC-4R agonist. Since the Claims of Group II are limited to the oral treatment of male erectile dysfunction with a human MC-4R agonist, they are considered to be separately patentable from those of Group I.

As will be set forth in detail below, Appellants submit that Appellants' specification fully teaches one skilled in the pertinent art how to make and how to practice the claimed invention as defined in Claims 39-73 and Claims 74-75, whereby the Board of Appeals should reverse the Examiner's rejections. Favorable action by the Board is respectfully requested.

Issue – Claims 39-73 and 74-75 contain subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which

it pertains to make and/or use the invention, and they are therefore rejected under 35 U.S.C. § 112, first paragraph.

The Examiner's Rationale

The Examiner's position is that the specification does not enable the ordinary practitioner of the pertinent art to choose a compound other than one specifically disclosed in the subject application, namely a substituted isoquinoline of structural formula I in the specification. The Examiner contends that there is no guidance provided as to what kind of compound to choose other than one of formula I and that extensive and undue experimentation would be required for the ordinary practitioner to randomly screen structurally undefined compounds to see if they are selective agonists of the human MC-4R according to the parameters disclosed in the Claims.

The §112, First Paragraph, Rejection is Improper

The examiner has misconstrued the nature of Applicants' invention. The Applicants have not invented any particular chemical compound, a class of structurally defined compounds, or methods of using a particular chemical compound or class of structurally defined compounds. Therefore, the requirements of § 112, first paragraph, for enablement support for claims to specific chemical compounds or uses thereof is not relevant. Rather the Appellants have discovered a specific physiological function for the human MC-4R, that is, its central nervous system control of sexual function. They have discovered a link between MC-4R agonism and induction of penile erections, that is, that selective activation of MC-4R can induce penile erections and consequently small molecule agonists of MC-4R have therapeutic utility to treat male erectile dysfunction (MED). Briefly, the Applicants have not invented compounds, but a novel method of treating erectile dysfunction in human males. Prior to Applicants' invention, the art taught only non-selective melanocortin receptor ligands for the treatment of MED, such as the compound MT-II, and even suggested that the erectogenic properties of melanotropic compounds was "probably mediated by a receptor other than the melanocortin-4 receptor" and "this other receptor could perhaps be the melanocortin-3 receptor" [A. Vergoni, European J. Pharmacol., 362: 95-101 (1998)]. At the time the Applicants' invention was made, the MC-4R was

appreciated to play an important role in the control of feeding rather than sexual behavior.

Therefore, the "critical reaction parameter" for method claims 39-73 and 74-75 is the function of selective activation of the human MC-4R. Applicants' specification clearly sets out a roadmap for the skilled artisan in the pharmacological arts to follow in order to identify compounds which bind selectively to MC-4R and which also function as agonists of MC-4R according to the parameters of Claims 39-75. The specification then proceeds to describe how to evaluate their therapeutic properties in several *in vivo* models of MED. The methods to be used to identify selective binders of MC-4R are presented on page 35 of the specification, which describes the assays that measure binding affinities to five different melanocortin receptor subtypes. Next the methods needed to determine whether the selective binders of MC-4R also function as selective agonists of MC-4R are provided by a description of the functional assays on page 37 of the specification. These functional assays are able to discriminate MC-4R agonists from antagonists. By a selective MC-4R agonist is meant a compound that binds to MC-4R and initiates a pharmacological response characteristic of only that receptor, that is, a compound that activates MC-4R and not the other four MC-R's. The ready availability of automated methods for drug screening, such as high-throughput screening (HTS), in the pharmaceutical industry allows for the routine screening of large chemical collections and libraries of chemical compounds to identify compounds with defined biological properties, such as selective activation of human MC-4R. This type of rapid and automated screening is well within the bounds of one of ordinary skill in the art of identifying biologically active compounds and does not require "extensive and undue experimentation." In fact, such assays are now routinely performed by programmed robots and can be set up to "tag" compounds that fall within the parameters of Claims 39-75. The process is not a random one. The Federal Circuit addressed the issue of amount of experimentation in *In re Wands* [8 USPQ2d 1400] as follows:

> Enablement is not precluded by the necessity for some experimentation such as **routine screening**. However,

> experimentation needed to practice the invention must not be undue experimentation. [8 USPQ2d at 1404]

"A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" [*In re Wands*, 8 USPQ2d at 1404] and "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance [*In re Colianni*, 195 USPQ at 153], which the Applicants have done in their specification. Time and difficulty of experiments are not determinative if they are merely routine (quoting from MPEP 2164.06). Wands, by its reference to routine screening as not constituting undue experimentation, clearly supports Applicants' position that the method claims of the instant invention are fully enabled.

Once the in vitro parameters of Claims 39-75 are satisfied, methods to use such MC-4R-selective agonists to treat MED are provided on pages 38-39 of the specification which describe the rat *ex copula* model of penile erection. Thus, how to identify ("make") and how to use compounds within the scope of Claims 39-75 are clearly set out in Applicants' specification. The identity of such compounds is not limited to, but is merely exemplified by, the isoquinoline compounds of the present application. Since the Applicants' specification enables the "critical or essential method parameters which are necessary to the practice of the invention," no undue experimentation is required other than carrying out what is taught in the specification. Example 84 constitutes a working example which clearly illustrates the operability of the present invention. The compound disclosed in Example 84 is representative of compounds that are selective agonists of human MC-4R within the parameters of the claims which induce penile erections in the rat when administered either by the oral or parenteral route.

Once a compound having the receptor binding and functional properties within the parameters of Claims 39-73 and 74-75 is identified, then the preparation of a pharmaceutical composition for systemic administration, as well as determining an appropriate dose and the route of administration, can be accomplished following the methods described in the instant application or modifications thereof which are known

to one of ordinary skill in the pharmaceutical arts. Although some experimentation may be necessary, the pharmaceutical arts typically engage in such activity in the drug discovery process.. The test of enablement is not whether any experimentation is necessary, but whether such necessary experimentation is undue (quoting from MPEP 2164.01). Thus, the Applicants submit that one reasonably skilled in the art could make/use the present invention from the disclosures in their specification coupled with information known in the art without undue experimentation.

Since the Applicants' specification does indeed teach one of ordinary skill how to identify selective MC-4R agonists and how to use them to treat MED, the Applicants submit that the enablement contained therein is fully commensurate in scope with Claims 39-73 and 74-75.

The patentability of functional claims without reference to chemical structure is supported by the consistent allowance by the U.S. Patent Office of such claims as in (a) U.S. Patent No. 6,469,012 with Claim 24 directed to a method of treating erectile dysfunction with a selective cGMP PDE-V inhibitor; (b) U.S. Patent No. 5,403,847 with claims directed to methods of treating benign prostatic hypertrophy with compounds that bind to the human α1c adrenergic receptor; and (c) U.S. Patent No. 6,048,850 with claims directed to a method for selectively inhibiting Cox-2 activity in a human with a non-steroidal compound that selectively inhibits activity of the Cox-2 gene product. The level of enablement provided by the patentees for the allowed functional claims in these U.S. patents is commensurate to that provided by the Applicants for the functional claims in the present application, that is, the Applicants' method claims 39-75 are in a breadth and format that have repeatably been found allowable by the U.S. Patent Office.

The Applicants have disclosed to the public a potentially medically useful approach for the treatment of erectile dysfunction based on a novel mechanism of action. They in turn should be granted claims that are commensurate with the significance and breadth of their invention.

SUMMARY

For the foregoing reasons, Appellants maintain that their specification fully enables one skilled in the art to make and use the claimed invention without undue

experimentation. It is therefore respectfully requested that the Board of Appeals reverse the Examiner's rejection of Claims 39-73 and 73-75 under 35 U.S.C. § 112, first paragraph.

Respectfully submitted,

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Date: February 6, 2003

APPPENDIX

Appeal Claims: Application Serial No.09/990,499

39. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human melanocortin-4 receptor (MC-4R) agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nanomolar (nM) and the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 30 nM.

40. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 100 nM.

41. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 1000 nM.

42. The method of Claim 39 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 2100 nM.

43. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nM and the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 30 nM.

44. The method of Claim 43 wherein the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 100 nM.

45. The method of Claim 43 wherein the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 540 nM.

46. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nM and the binding of the compound to the human MC-5R is characterized by an IC_{50} greater than 30 nM.

47. The method of Claim 46 wherein the binding of the compound to the human MC-5R is characterized by an IC_{50} of greater than 100 nM.

48. The method of Claim 46 wherein the binding of the compound to the human MC-5R is characterized by an IC_{50} greater than 230 nM.

49. The method of Claim 39 wherein the compound is further characterized by binding to each of the human MC-2R, MC-3R, and MC-5R with an IC_{50} greater than 30 nM.

50. The method of Claim 40 wherein the compound is further characterized by binding to each of the human MC-2R, MC-3R, and MC-5R with an IC_{50} greater than 100 nM.

51. The method of Claim 41 wherein the compound is further characterized by binding to each of the human MC-2R and MC-3R with an IC_{50} greater than 540 nM and binding to the MC-5R with an IC_{50} greater than 230 nM.

52. The method of Claim 49 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 30 nM.

53. The method of Claim 50 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 100 nM.

54. The method of Claim 51 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 500 nM.

55. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the compound binds to the human MC-4R with a binding affinity at least 10-fold higher than the compound binds to each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

56. The method of Claim 55 wherein the compound binds to the human MC-4R with a binding affinity at least 100-fold higher than the compound binds to each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

57. The method of Claim 55 wherein the compound binds to the human MC-4R with a binding affinity at least 1000-fold higher than the compound binds to each of the human MC-1R and MC-2R, at least 580-fold higher than the compound binds to the human MC-3R, and at least 250-fold higher than the compound binds to the human MC-5R.

58. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the compound binds to the human MC-4R with a binding affinity at least 10-fold higher than the compound binds to any other human melanocortin receptor.

59. The method of Claim 58 wherein the compound binds to the human MC-4R with a binding affinity at least 100-fold higher than the compound binds to any other human melanocortin receptor.

60. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-1R is characterized by an EC_{50} greater than 10 nM.

61. The method of Claim 60 wherein the functional activity of the compound at the MC-1R is characterized by an EC_{50} greater than 100 nM.

62. The method of Claim 60 wherein the functional activity of the compound at the MC-1R is characterized by an EC_{50} greater than 1200 nM.

63. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-3R is characterized by an EC_{50} greater than 10 nM.

64. The method of Claim 63 wherein the functional activity of the compound at the MC-3R is characterized by an EC_{50} greater than 100 nM.

65. The method of Claim 63 wherein the functional activity of the compound at the MC-3R is characterized by an EC_{50} greater than 1200 nM.

66. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-5R is characterized by an EC_{50} greater than 10 nM.

67. The method of Claim 66 wherein the functional activity of the compound at the MC-5R is characterized by an EC_{50} greater than 100 nM.

68. The method of Claim 66 wherein the functional activity of the compound at the MC-5R is characterized by an EC_{50} greater than 520 nM.

69. The method of Claim 60 wherein the compound is further characterized by having a functional activity at each of the human MC-2R, MC-3R, and MC-5R with an EC_{50} greater than 10 nM.

70. The method of Claim 61 wherein the compound is further characterized by having a functional activity at each of the human MC-2R, MC-3R, and MC-5R with an EC_{50} greater than 100 nM.

71. The method of Claim 62 wherein the compound is further characterized by having a functional activity at the human MC-2R and MC-3R with an EC_{50} greater than 1200 nM and a functional activity at the human MC-5R with an EC_{50} greater than 520 nM.

72. A method of treating erectile dysfunction in a male subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 10-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

73. The method of Claim 72 wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 100-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

74. A method for the oral treatment of erectile dysfunction in a male subject which comprises the oral administration to the subject in need thereof a therapeutically effective amount of a compound which is an agonist of the human MC-4R.

75. The method of Claim 74 wherein the compound is a selective agonist of the human MC-4R.

U. S. Patent and Tr... rk Office: U.S. DEPARTMENT OF COMMERCE
SUBSTITUTE for PTO/SB/17(01-03)"FEE TRANSMITTAL for FY 2003"

FEE TRANSMITTAL

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT	$430

Complete if Known	
Application Number	09/990,499
Filing Date	November 21, 2001
First Named Inventor	Raman K. Bakshi, et al.
Examiner Name	D. M. Seaman
Group Art Unit	1625
Attorney Docket Number	20385YDA

#7

METHOD OF PAYMENT (Check one)

☒ Deposit Account

Deposit Account Number: 13-2755

Deposit Account Name: Merck & Co., Inc.

The Commissioner is authorized to:

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) during the pendency of this application

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Fee ($)	Fee Description	Fee Paid
1001	750	Utility filing fee	
1002	330	Design filing fee	
1004	750	Reissue filing fee	
1005	160	Provisional filing fee	

SUBTOTAL(1) $0

2. EXTRA CLAIM FEES

			Extra		Fee from below	Fee Paid
Total Claims		- 20 ** =	0	x	$18 =	0
Independent Claims		- 3 ** =	0	x	$84 =	0
Multiple Dependent Claims					$280 =	

***or number previously paid, if greater; For Reissues, see below*

Large Entity Fee Code	Fee ($)	Fee Description
1202	18	Claims in excess of 20
1201	84	Independent claims in excess of 3
1203	280	Multiple dependent claim, if not paid
1204	84	**Reissue independent claims over original patent
1205	18	**Reissue claims in excess of 20 and over original patent

SUBTOTAL(2) $0

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Fee ($)	Fee Description	Fee Paid
1051	130	Surcharge - late filing fee or oath	
1812	2,520	For filing a request for *ex parte* reexamination	
1251	110	Extension for reply within first month	110
1252	410	Extension for reply within second month	
1253	930	Extension for reply within third month	
1254	1,450	Extension for reply within fourth month	
1255	1,970	Extension for reply within fifth month	
1401	320	Notice of Appeal	
1402	320	Filing a brief in support of an appeal	320
1403	280	Request for oral hearing	
1452	110	Petition to revive - unavoidable	
1453	1,300	Petition to revive - unintentional	
1501	1,300	Utility issue fee (or reissue)	
1502	470	Design issue fee	
1460	130	Petitions to the Commissioner	
1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	Submission of Information Disclosure Statement	
8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	For each additional invention to be examined (37 CFR 1.129(b))	
1801	750	Request for Continued Examination (RCE)	
Other fee (specify)			
Other fee (specify)			

SUBTOTAL(3) $430

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SUBMITTED BY

Typed or Printed Name	Melvin Winokur	Date	02/05/2003	Reg. Number	32,763
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Complete (if applicable)

Application Number:	09/990,499
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First Named Inventor:	Raman K. Bakshi, et al.
Group Art Unit:	1625
Examiner Name:	D. M. Seaman
Attorney Docket Number:	20385YDA

FIRST CLASS MAIL CERTIFICATE

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231, ON THE DATE APPEARING BELOW.

MERCK & CO., INC.

MAILED BY Denise K. Brown DATE 02/06/2003